Attorney Docket No.: RTS-0341
Inventors: Graham and Dobie
Serial No.: 10/006,430
Filing Date: December 10, 2001
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REMARKS

Claims 1-10, 12-15 and 21-32 are pending in the instant application. Claims 1, 2, 4-10 and 12-15 have been rejected. Claims 3 and 21-32 have been objected to. Claim 1 has been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 102

Claims 1, 2, 12 and 14 have been rejected under 35 U.S.C. 102(b) as being anticipated by N_Geneseq database AAX37224. The Examiner suggests that the cited sequence is a 38 mer sequence having bases 820-845 of instant SEQ ID NO: 3 and would inherently be expected to function as antisense due to the base homology. Applicants respectfully traverse this rejection.

At the outset, Applicants have amended claim 1 to recite that the compounds of the instant invention are targeted to nucleobase regions within the coding region of SEQ ID NO: 3 that do not include nucleobases 820 through 845. Support for this amendment can be found throughout the specification as filed, in particular at pages 82-83. In order to anticipate a claim, the reference must recite each and every limitation of the claim (MPEP 2131). Since

the cited gene sequence AAX37224 targets nucleobases 820-845, the reference cannot anticipate the claims as amended. Withdrawal of this rejection is respectfully requested.

Claims 1, 2, 12 and 14 have been rejected under 35 U.S.C. 102(b) as being anticipated by GenEMBL AX004400. The Examiner suggests that the cited sequence is a 26 mer sequence that has bases 820-845 of instant SEQ ID NO: 3. Applicants respectfully traverse this rejection.

As discussed *supra*, Applicants have amended the claims to recite that they are drawn to antisense compounds that are targeted to specific regions of CD81 nucleic acid molecules that do not consist of the portion of the sequence cited by the Examiner. Therefore, this citation cannot anticipate the claims as amended as it fails to teach the limitations of the claims, which specify regions of CD81 nucleic acid molecules other than nucleobases 820-845. Accordingly, withdrawal of this rejection is respectfully requested.

II. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2, 4-10 and 12-15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Oren et al. (1990) and Tsitsikov et al. (1997), in view of Iurlaro et al. (2000), Bennett et al.

(1996), Baracchini et al. (US Patent 5,801,154), and Cowsert et al. (US Patent 5,951,455). The Examiner suggests that it would have been *prima facie* obvious for one of ordinary skill in the art to design antisense to the CD81 gene as taught by Oren et al. (1990) in order to investigate the protein function as suggested by Agrawal et al., for the identification of drug candidates as taught by Bennett et al. The Examiner suggests that one of skill would have been motivated to inhibit CD81 since Tsitsikov et al. teach inhibition of this gene has specific physiologic effects and since Agrawal et al., Bennett et al., and Cowsert et al. teach the benefits of antisense for study of gene function in cells, while these same references provide one of skill with the motivation to modify antisense as claimed. The Examiner suggests that an expectation of success is provided by the teachings of Bennett et al., Agrawal et al., Cowsert et al., and Baracchini et al. in teaching that design of antisense requires the target gene sequence and modification to optimize activity. Applicants respectfully traverse this rejection.

Oren et al. (1990) disclose the cloning of human CD81 and its mapping to chromosome 11p15.5. Nowhere does this reference teach or suggest antisense compounds of any size targeted to human CD81 nucleic acid molecules as claimed or the use of such compounds to

inhibit expression of human CD81. The reference also fails to teach specific regions of human CD81 nucleic acid molecules that could be targeted successfully with antisense compounds and result in inhibition of gene expression.

Tsitsikov et al. (1997) disclose that CD81 is important for CD19 signaling and B cell function in a mouse model of CD81-deficient gene expression. Nowhere does this reference teach or suggest antisense compounds of any size targeted to human CD81 nucleic acid molecules as claimed or the use of such compounds to inhibit expression of human CD81. The reference also fails to teach specific regions of human CD81 nucleic acid molecules that could be targeted successfully with antisense compounds and result in inhibition of gene expression.

The secondary references cited fail to overcome the deficiencies in teaching of these primary references when considered together.

Agrawal et al. (2000) is a review of the state of the art of antisense technology. Although the paper discusses that antisense in theory can be developed to any target gene, when the paper is read in its entirety, it is clear that there are many obstacles that must be considered in order to develop pharmacologically active antisense compounds, above knowing the sequence of a target

gene. Therefore, contrary to the Examiner's suggestion, this paper does not teach one of skill, nor suggest that one of skill should expect that antisense compounds to any target gene would have activity to inhibit gene expression. Nowhere does this reference teach or suggest antisense compounds of any size targeted to human CD81 nucleic acid molecules as claimed or the use of such compounds to inhibit expression of human CD81. The reference also fails to teach specific regions of human CD81 nucleic acid molecules that could be targeted successfully with antisense compounds and result in inhibition of gene expression. It is only with the specification in hand that one of skill would know which specific regions of human CD81 nucleic acid molecules could be successfully targeted with antisense compounds and result in inhibition of gene expression.

Bennett et al. (1996) is another review paper on the technology of antisense. Although the paper suggests that antisense offers the opportunity to identify lead compounds based on knowledge of biology and a relevant gene target sequence, the paper also states in the introduction that the field is still early in its stages and there are key questions that need to be answered and technical hurdles to overcome. Therefore, contrary to the Examiner's suggestion, the paper does not provide one of skill with

the motivation to target any gene sequence as they state that the technology still has unresolved problems. Further, nowhere does this reference teach or suggest antisense compounds of any size targeted to human CD81 nucleic acid molecules as claimed or the use of such compounds to inhibit expression of human CD81. The reference also fails to teach specific regions of human CD81 nucleic acid molecules that could be targeted successfully with antisense compounds and result in inhibition of gene expression.

The patents of Cowsert et al. and Baracchini et al. disclose the use of antisense modifications as a way to enhance antisense activity in general. However, neither of these patents teach or suggest antisense compounds of any size targeted to human CD81 nucleic acid molecules as claimed or the use of such compounds to inhibit expression of human CD81. The references also fail to teach specific regions of human CD81 nucleic acid molecules that could be targeted successfully with antisense compounds and result in inhibition of gene expression.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.

Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the combination of prior art cited fails to teach or suggest the limitations of the claims as amended, which claim antisense compounds targeted to specific regions of nucleic acid molecules encoding human CD81, and thus cannot render the instant claimed invention obvious. Although the references when combined may teach that antisense can be designed to genes of known sequence, it is only with the specification in hand that one of skill would have an expectation of success at targeting the specific regions within the sequence of human CD81 nucleic acid molecules as claimed. The mere teaching of a gene sequence and the concept of antisense does not provide one of skill with the motivation nor the expectation of success at developing the antisense compounds as claimed which are specific compounds targeted to specific regions within human CD81 nucleic acid molecules. Accordingly, this combination of references cannot establish a prima facie case of obviousness. Withdrawal of this rejection is therefore respectfully requested.

III. Objection to the Claims

Claims 3 and 21-32 have been objected to as being dependent on a rejected base claim but the Examiner suggests they would be allowable if rewritten in independent form including all of the limitations of the base claims. Applicants respectfully point out that claim 3 was amended to be independent in the previous reply dated July 2, 2002, with claims 21-32 added as claims dependent on newly independent claim 3. Since there is no rejection of record pertaining to claims 3 or 21-32, Applicants have not amended these claims further. Accordingly, withdrawal of this objection is respectfully requested.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

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Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 1 has been amended as follows:

1. (twice amended) A compound 16 to 50 nucleobases in length targeted to a 3'-untranslated region, nucleobases 246 through 265, nucleobases 272 through 339, nucleobases 375 through 394, nucleobases 402 through 429, nucleobases 471 through 490, nucleobases 497 through 516, nucleobases 536 through 555, nucleobases 564 through 626, nucleobases 665 through 697, nucleobases 747 through 772, nucleobases 781 through 809, or nucleobases 848 through 934 of a coding region, a stop codon region, or a 3'-untranslated region of a nucleic acid molecule encoding CD81 of SEQ ID NO: 3, an intron 1 region, an intron 2 region, an intron 3 region, and intron:exon junction region, an exon 1 region, or an exon 3 region of a nucleic acid molecule encoding human CD81 of SEQ ID NO: 11, or a 3'-untranslated region of a nucleic acid molecule encoding human CD81 of SEQ ID NO: 10, wherein said compound specifically hybridizes with one of said regions of said nucleic acid molecule encoding CD81 and inhibits the expression of CD81.